Lupin Pharmaceuticals, Inc.

Dockets Management Branch
Food and Drug Administration
Department of Health and Human Services
HFA-305, Room 1061
5630 Fishers Lane
Rockville, MD 20852

SUITABILITY PETITION

This petition is submitted pursuant to 21 CFR 10.20 and 10.30, as provided for in 21 CFR 314.93 and Section 505(j)(2)(c) of the Federal Food, Drug and Cosmetic Act, to request the Commissioner of the Food and Drug Administration to declare that the drug product Cefixime Chewable Tablets, 100 mg, 150 mg and 200 mg are suitable for submission as an abbreviated new drug application (ANDA).

A. Action Requested

The petition is submitted for changes in dosage form and strength [from "powder for oral suspension, 100 mg/5 mL" to "Chewable Tablets, 100 mg, 150 mg and 200 mg] from that of the reference listed drug product, Suprax® (cefixime) for Oral Suspension 100 mg/5 mL, manufactured by Lupin Limited. Cefixime Chewable Tablets will be marketed in dosage strengths of 100 mg, 150 mg and 200 mg. The drug, the route of administration and the dosage regimen for use apart from differences explained under "statement of grounds" followed, are the same as the reference listed drug product.

B. Statement of Grounds

The recommended dose of Suprax® (cefixime) for Oral Suspension is 8 mg/kg/day. This may be administered as a single daily dose or may be given in two divided doses, as 4 mg/kg every 12 hours.

2004P.0263

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HARBORPLACE TOWER, 111 SOUTH CALVERT STREET, 21ST FLOOR, BALTIMORE, MD 21202 TEL 410-576-2000 FAX 410-576-2221

The requested change in strength should not raise any questions regarding safety or efficacy as the proposed strengths for Cefixime Chewable Tablets (i.e. 100 mg, 150 mg and 200 mg) represent intermediate strengths between the already approved lowest (50 mg) and highest (400 mg) dosage regimen of Suprax® (cefixime) for Oral Suspension.

Cefixime Chewable Tablets 100 mg are appropriate for a 100 mg dose, Cefixime Chewable Tablets 150 mg are appropriate for a 150 mg dose and Cefixime Chewable Tablets 200 mg are appropriate for a 200 mg dose.

Additionally, Cefixime Chewable Tablets are expected to offer a better alternative to the powder for oral suspension due to the following advantages:

- Unit dose dispensing
- Convenience to the patient with respect to the ease of administration, even during travel
- Storage of the product will not require special conditions (e.g., refrigeration)
- Ease of carrying
- Better precision of dosage over the traditional teaspoonful
- This will lead to better patient compliance

The proposed drug product is expected to demonstrate bioequivalence to the reference listed drug product - Suprax® (cefixime) for Oral Suspension 100 mg/5 mL; data will be submitted at a later date.

Labeling of the proposed product (provided as **Enclosure 1**) will be the same as that of the reference listed drug product (provided as **Enclosure 2**) with differences explained above.

Further, the petitioner intends to collaborate closely with the Agency on the labeling and package insert of the proposed product to assure the safety and effectiveness of this product.

C. Pediatric Use Information

As the package insert of Lupin Limited's Suprax® (cefixime) for Oral Suspension contains adequate dosing and administration information for the pediatric population, no additional studies are required.

D. Environmental Impact

An environmental assessment report on the action requested in this petition is not required under 21 CFR 25.31.

E. Economic Impact

The petitioner does not believe that this is applicable in this case, but will agree to provide such an analysis if requested by the agency.

F. Certification

The undersigned certifies that to the best of his knowledge, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

Sincerely,

For Lupin Limited,

VINITA GUPTA
President - Lupin Pharmaceuticals, Inc.

Enclosures - As above

cc **Mr. Gary Buehler, Director, Office of Generic Drugs**

ENCLOSURE 1

Labeling of the Proposed Product –
Cefixime Chewable Tablets 100 mg, 150 mg, 200 mg

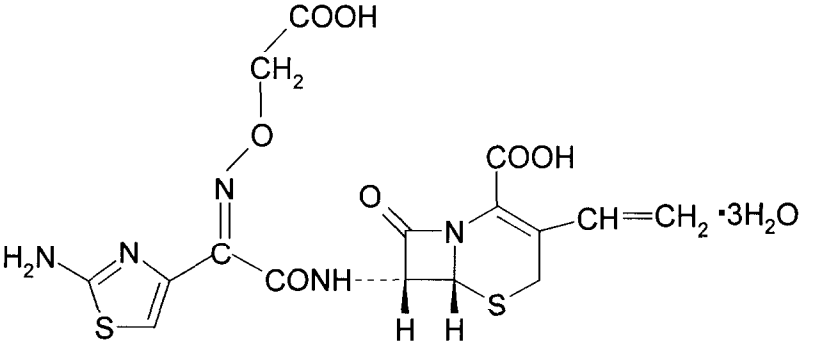
CEFIXIME CHEWABLE TABLETS
Rx only

To reduce the development of drug-resistant bacteria and maintain the effectiveness of cefixime chewable tablets and other antibacterial drugs, cefixime chewable tablets should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

DESCRIPTION

Cefixime chewable tablets is a semisynthetic, cephalosporin antibiotic for oral administration. Chemically, it is (*6R, 7R*)-7-[2-(2-Amino-4-thia-zolyl)glyoxylamido]-8-oxo-3-vinyl-5-thia-1-azabicyclo[4.2.0] oct-2-ene-2-carboxylic acid, 7^2-(*Z*)-[*O*-(carboxymethyl) oxime] trihydrate. Molecular weight = 507.50 as the trihydrate.

The structural formula for cefixime is:



Each chewable tablet contains either 100 mg, 150 mg or 200 mg of cefixime as the trihydrate.

Inactive ingredients will be furnished when ANDA is submitted, since this is proprietary information. The inactives are GRAS ingredients at appropriate levels.

CLINICAL PHARMACOLOGY

Cefixime chewable tablets are bioequivalent to oral suspension.

Cefixime chewable tablets or oral suspension, given orally, is about 40%-50% absorbed whether administered with or without food; however, time to maximal absorption is increased approximately 0.8 hours when administered with food. Cefixime chewable tablets or oral suspension produces average peak concentrations approximately 25%-50% higher than the tablets, when tested in normal *adult* volunteers. Two hundred and 400 mg doses of cefixime chewable tablets or oral suspension produce average peak concentrations of 3 mcg/mL (range 1 to 4.5 mcg/mL) and 4.6 mcg/mL (range 1.9 to 7.7 mcg/mL), respectively, when tested in normal *adult* volunteers. The area under the time versus concentration curve is greater by approximately 10%-25% with the cefixime chewable tablets or oral suspension than with the tablet after doses of 100 to 400 mg, when tested in normal *adult* volunteers. This increased absorption should be taken into consideration if the cefixime chewable tablets or oral suspension is to be substituted for the tablet. Because of the lack of bioequivalence, tablets should not be substituted for cefixime chewable tablets or oral suspension in the treatment of otitis media. (See DOSAGE AND ADMINISTRATION). Cross-over studies of tablet versus chewable tablets or suspension have not been performed in children.

Peak serum concentrations occur between 2 and 6 hours following oral administration of 400 mg of cefixime chewable tablets or cefixime suspension.

Peak serum concentrations occur between 2 and 5 hours following a single administration of 200 mg of chewable tablets or suspension.

TABLE

Serum Levels of Cefixime after Administration of Tablets (mcg/mL)							
DOSE	**1h**	**2h**	**4h**	**6h**	**8h**	**12h**	**24h**
100 mg	0.3	0.8	1	0.7	0.4	0.2	0.02
200 mg	0.7	1.4	2	1.5	1	0.4	0.03
400 mg	1.2	2.5	3.5	2.7	1.7	0.6	0.04
Serum Levels of Cefixime after Administration of Chewable Tablets or Oral Suspension (mcg/mL)							
DOSE	**1h**	**2h**	**4h**	**6h**	**8h**	**12h**	**24h**
100 mg	0.7	1.1	1.3	0.9	0.6	0.2	0.02
200 mg	1.2	2.1	2.8	2	1.3	0.5	0.07
400 mg	1.8	3.3	4.4	3.3	2.2	0.8	0.07

Approximately 50% of the absorbed dose is excreted unchanged in the urine in 24 hours. In animal studies, it was noted that cefixime is also excreted in the bile in excess of 10% of the administered dose. Serum protein binding is concentration independent with a bound fraction of approximately 65%. In a multiple dose study conducted with a research formulation which is less bioavailable than the tablet or suspension, there was little accumulation of drug in serum or urine after dosing for 14 days. The serum half-life of cefixime in healthy subjects is independent of dosage form and averages 3-4 hours but may range up to 9 hours in some normal volunteers. Average AUCs at steady state in elderly patients are approximately 40% higher than average AUCs in other healthy adults.

In subjects with moderate impairment of renal function (20 to 40 mL/min creatinine clearance), the average serum half-life of cefixime is prolonged to 6.4 hours. In severe renal impairment (5 to 20 mL/min creatinine clearance), the half-life increased to an average of 11.5 hours. The drug is not cleared significantly from the blood by hemodialysis or peritoneal dialysis. However, a study indicated that with doses of 400 mg, patients undergoing hemodialysis have similar blood profiles as subjects with creatinine clearances of 21-60 mL/min. There is no evidence of metabolism of cefixime *in vivo*.

Adequate data on CSF levels of cefixime are not available.

Microbiology

As with other cephalosporins, bactericidal action of cefixime results from inhibition of cell-wall synthesis. Cefixime is highly stable in the presence of beta-lactamase enzymes. As a result, many organisms resistant to penicillins and some cephalosporins due to the presence of beta-lactamases, may be susceptible to cefixime. Cefixime has been shown to be active against most strains of the following organisms both *in vitro* and in clinical infections (see **INDICATIONS AND USAGE**):

Gram-positive Organisms.
Streptococcus pneumoniae,
Streptococcus pyogenes.
Gram-negative Organisms.
Haemophilus influenzae
(beta-lactamase positive and negative strains),
Moraxella (Branhamella) catarrhalis
(most of which are beta-lactamase positive),
Escherichia coli,
Proteus mirabilis,
Neisseria gonorrhoeae
(including penicillinase- and non-penicillinase-producing strains).

Cefixime has been shown to be active *in vitro* against most strains of the following organisms; however, clinical efficacy has not been established.

Gram-positive Organisms.
Streptococcus agalactiae.
Gram-negative Organisms.
Haemophilus parainfluenzae
(beta-lactamase positive and negative strains),
Proteus vulgaris,
Klebsiella pneumoniae,
Klebsiella oxytoca,
Pasteurella multocida,
Providencia species,
Salmonella species,
Shigella species,
Citrobacter amalonaticus,
Citrobacter diversus,
Serratia marcescens.

Note: *Pseudomonas* species, strains of group D streptococci (including enterococci), *Listeria monocytogenes*, most strains of staphylococci (including methicillin-resistant strains) and most strains of *Enterobacter* are resistant to cefixime. In addition, most strains of *Bacteroides fragilis* and *Clostridia* are resistant to cefixime.

Susceptibility Testing
Susceptibility Tests:
Diffusion Techniques
Quantitative methods that require measurement of zone diameters give an estimate of antibiotic susceptibility. One such procedure[1-3] has been recommended for use with disks to test susceptibility to cefixime. Interpretation involves correlation of the diameters obtained in the disk test with minimum inhibitory concentration (MIC) for cefixime.

Reports from the laboratory giving results of the standard single-disk susceptibility test with a 5-mcg cefixime disk should be interpreted according to the following criteria:

Recommended Susceptibility Ranges: Agar Disk Diffusion			
Organisms	**Resistant**	**Moderately Susceptible**	**Susceptible**
Neisseria gonorrhoeae[a]	--	--	≥ 31 mm
All other organisms	≤ 15 mm	16 - 18 mm	≥ 19 mm
[a] Using GC Agar Base with a defined 1% supplement without cysteine.			

A report of "Susceptible" indicates that the pathogen is likely to be inhibited by generally achievable blood levels. A report of "Moderately Susceptible" indicates that inhibitory concentrations of the antibiotic may well be achieved if high dosage is used or if the infection is confined to tissues and fluids (e.g. urine) in which high antibiotic levels are attained. A report of "Resistant" indicates that achievable concentrations of the antibiotic are unlikely to be inhibitory and other therapy should be selected.

Standardized procedures require the use of laboratory control organisms. The 5-mcg disk should give the following zone diameter:

Organism	Zone diameter (mm)
E. coli ATCC 25922	23-27
N. gonorrhoeae ATCC 49226[a]	37-45

[a] Using GC Agar Base with a defined 1% supplement without cysteine.

The class disk for cephalosporin susceptibility testing (the cephalothin disk) is not appropriate because of spectrum differences with cefixime. The 5-mcg cefixime disk should be used for all in vitro testing of isolates.

Dilution Techniques

Broth or agar dilution methods can be used to determine the minimum inhibitory concentration (MIC) value for susceptibility of bacterial isolates to cefixime. The recommended susceptibility breakpoints are as follows:

MIC Interpretive Standards (mcg/mL)			
Organisms	**Resistant**	**Moderately Susceptible**	**Susceptible**
Neisseria gonorrhoeae[a]	--	--	≤ 0.25
All other organisms	≥ 4	2	≤ 1

As with standard diffusion methods, dilution procedures require the use of laboratory control organisms. Standard cefixime powder should give the following MIC ranges in daily testing of quality control organisms:

Organism	MIC range (mcg/mL)
E. coli ATCC 25922	0.25-1
S. aureus ATCC 29213	8-32
N. gonorrhoeae ATCC 49226[a]	0.008-0.03

[a] Using GC Agar Base with a defined 1% supplement without cysteine.

INDICATIONS AND USAGE

To reduce the development of drug resistant bacteria and maintain the effectiveness of cefixime chewable tablets and other antibacterial drugs, cefixime chewable tablets should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antimicrobial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

Cefixime chewable tablets is indicated in the treatment of the following infections when caused by susceptible strains of the designated microorganisms:

Uncomplicated Urinary Tract Infections caused by *Escherichia coli* and *Proteus mirabilis*.

Otitis Media caused by *Haemophilus influenzae* (beta-lactamase positive and negative strains), *Moraxella (Branhamella) catarrhalis*, (most of which are beta-lactamase positive) and *S. pyogenes**.
Note: For information on *otitis media* caused by *Streptococcus pneumoniae*, see **CLINICAL STUDIES** section.

Pharyngitis and Tonsillitis, caused by S. pyogenes.
Note: Penicillin is the usual drug of choice in the treatment of S. pyogenes infections, including the prophylaxis of rheumatic fever. Cefixime chewable tablets is generally effective in the eradication of S. pyogenes from the nasopharynx; however, data establishing the efficacy of cefixime chewable tablets in the subsequent prevention of rheumatic fever are not available.

Acute Bronchitis and *Acute Exacerbations of Chronic Bronchitis*, caused by *Streptococcus pneumoniae* and *Haemophilus influenzae* (beta-lactamase positive and negative strains).

Uncomplicated gonorrhea (cervical/urethral), caused by *Neisseria gonorrhoeae* (penicillinase-and non-penicillinase- producing strains).

Appropriate cultures and susceptibility studies should be performed to determine the causative organism and its susceptibility to cefixime; however, therapy may be started while awaiting the results of these studies. Therapy should be adjusted, if necessary, once these results are known.

* Efficacy for this organism in this organ system was studied in fewer than 10 infections.

CLINICAL STUDIES

In clinical trials of otitis media in nearly 400 children between the ages of 6 months to 10 years, *Streptococcus pneumoniae* was isolated from 47% of the patients, *Haemophilus influenzae* from 34%, *Moraxella (Branhamella) catarrhalis* from 15% and *S. pyogenes* from 4%.

The overall response rate of *Streptococcus pneumoniae* to cefixime was approximately 10% lower and that of *Haemophilus influenzae* or *Moraxella (Branhamella) catarrhalis* approximately 7% higher (12% when beta-lactamase positive strains of *H. influenzae* are included) than the response rates of these organisms to the active control drugs.

In these studies, patients were randomized and treated with either cefixime at dose regimens of 4 mg/kg BID or 8 mg/kg QD, or with a standard antibiotic regimen. Sixty-nine to 70% of the patients in each group had resolution of signs and symptoms of otitis media when evaluated 2 to 4 weeks post-treatment, but persistent effusion was found in 15% of the patients. When evaluated at the completion of therapy, 17% of patients receiving cefixime and 14% of patients receiving effective comparative drugs (18% including those patients who had *Haemophilus influenzae* resistant to the control drug and who received the control antibiotic) were considered to be treatment failures. By the 2 to 4 week follow-up, a total of 30%-31% of patients had evidence of either treatment failure or recurrent disease.

Bacteriological Outcome of Otitis Media at Two to Four Weeks Post-Therapy Based on Repeat Middle Ear Fluid Culture or Extrapolation from Clinical Outcome

Organism	Cefixime(a) 4 mg/kg BID	Cefixime(a) 8 mg/kg QD	Control(a) drugs
Streptococcus pneumoniae	48/70 (69%)	18/22 (82%)	82/100 (82%)
Haemophilus influenzae beta-lactamase negative	24/34 (71%)	13/17 (76%)	23/34 (68%)
Haemophilus influenzae beta-lactamase positive	17/22 (77%)	9/12 (75%)	1/1 (b)
Moraxella (Branhamella) catarrhalis	26/31 (84%)	5/5	18/24 (75%)
S. pyogenes	5/5	3/3	6/7
All Isolates	120/162 (74%)	48/59 (81%)	130/166 (78%)

(a) Number eradicated/number isolated.

(b) An additional 20 beta-lactamase positive strains of *Haemophilus influenzae* were isolated, but were excluded from this analysis because they were resistant to the control antibiotic. In nineteen of these, the clinical course could be assessed and a favorable outcome occurred in 10. When these cases are included in the overall bacteriological evaluation of therapy with the control drugs, 140/185 (76%) of pathogens were considered to be eradicated.

CONTRAINDICATIONS

Cefixime chewable tablets is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

WARNINGS

BEFORE THERAPY WITH CEFIXIME CHEWABLE TABLETS IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE TO DETERMINE WHETHER THE PATIENT HAS HAD PREVIOUS HYPERSENSITIVITY REACTIONS TO CEPHALOSPORINS, PENICILLINS, OR OTHER DRUGS. IF THIS PRODUCT IS TO BE GIVEN TO PENICILLIN-SENSITIVE PATIENTS, CAUTION SHOULD BE EXERCISED BECAUSE CROSS HYPERSENSITIVITY AMONG BETA-LACTAM ANTIBIOTICS HAS BEEN CLEARLY DOCUMENTED AND MAY OCCUR IN UP TO 10% OF PATIENTS WITH A HISTORY OF PENICILLIN ALLERGY. IF AN ALLERGIC REACTION TO CEFIXIME CHEWABLE TABLETS OCCURS, DISCONTINUE THE DRUG. SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE TREATMENT WITH EPINEPHRINE AND OTHER EMERGENCY MEASURES, INCLUDING OXYGEN, INTRAVENOUS FLUIDS, INTRAVENOUS ANTIHISTAMINES, CORTICOSTEROIDS, PRESSOR AMINES AND AIRWAY MANAGEMENT, AS CLINICALLY INDICATED.

Anaphylactic/anaphylactoid reactions (including shock and fatalities) have been reported with the use of cefixime.

Antibiotics, including cefixime chewable tablets, should be administered cautiously to any patient who has demonstrated some form of allergy, particularly to drugs.

Treatment with broad spectrum antibiotics, including cefixime chewable tablets, alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by Clostridium difficile is a primary cause of severe antibiotic-associated diarrhea including pseudomembranous colitis.

Pseudomembranous colitis has been reported with the use of cefixime chewable tablets and other broad-spectrum antibiotics (including macrolides, semisynthetic penicillins, and cephalosporins); therefore, it is important to consider this diagnosis in patients who develop diarrhea in association with the use of antibiotics. Symptoms of pseudomembranous colitis may occur during or after antibiotic treatment and may range in severity from mild to life-threatening. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, management should include fluids, electrolytes, and protein supplementation. If the colitis does not improve after the drug has been discontinued, or if the symptoms are severe, oral vancomycin is the drug of choice for antibiotic-associated pseudomembranous colitis produced by *C. difficile*. Other causes of colitis should be excluded.

PRECAUTIONS

General

Prescribing cefixime chewable tablets in the absence of a proven or strongly suspected bacterial infection of a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

The possibility of the emergence of resistant organisms which might result in overgrowth should be kept in mind, particularly during prolonged treatment. In such use, careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.

The dose of cefixime chewable tablet should be adjusted in patients with renal impairment as well as those undergoing continuous ambulatory peritoneal dialysis (CAPD) and hemodialysis (HD). Patients on dialysis should be monitored carefully. (See **DOSAGE AND ADMINISTRATION**.)

Cefixime chewable tablets should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis.

Drug Interactions

Carbamazepine: Elevated carbamazepine levels have been reported in postmarketing experience when cefixime is administered concomitantly. Drug monitoring may be of assistance in detecting alterations in carbamazepine plasma concentrations.

Warfarin and Anticoagulants: Increased prothrombin time, with or without clinical bleeding, has been reported when cefixime is administered concomitantly.

Drug/Laboratory Test Interactions

A false-positive reaction for ketones in the urine may occur with tests using nitroprusside but not with those using nitroferricyanide.

The administration of cefixime may result in a false-positive reaction for glucose in the urine using Clinitest®**, Benedict's solution, or Fehling's solution. It is recommended that glucose tests based on enzymatic glucose oxidase reactions (such as Clinistix®** or TesTape®**) be used.

A false-positive direct Coombs test has been reported during treatment with other cephalosporin antibiotics; therefore, it should be recognized that a positive Coombs test may be due to the drug.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Lifetime studies in animals to evaluate carcinogenic potential have not been conducted. Cefixime did not cause point mutations in bacteria or mammalian cells, DNA damage, or chromosome damage *in vitro* and did not exhibit clastogenic potential *in vivo* in the mouse micronucleus test. In rats, fertility and reproductive performance were not affected by cefixime at doses up to 125 times the adult therapeutic dose.

Usage in Pregnancy

Pregnancy Category B. Reproduction studies have been performed in mice and rats at doses up to 400 times the human dose and have revealed no evidence of harm to the fetus due to cefixime. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery
Cefixime has not been studied for use during labor and delivery. Treatment should only be given if clearly needed.

Nursing Mothers
It is not known whether cefixime is excreted in human milk. Consideration should be given to discontinuing nursing temporarily during treatment with this drug.

Pediatric Use
Safety and effectiveness of cefixime in children aged less than six months old have not been established.
The incidence of gastrointestinal adverse reactions, including diarrhea and loose stools, in the pediatric patients receiving the suspension, was comparable to the incidence seen in adult patients receiving tablets.

Information for Patients
Patients should be counseled that antibacterial drugs, including cefixime chewable tablets, should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When cefixime chewable tablets is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may: (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by cefixime chewable tablets or other antibacterial drugs in the future.

ADVERSE REACTIONS
Most of adverse reactions observed in clinical trials were of a mild and transient nature. Five percent (5%) of patients in the U.S. trials discontinued therapy because of drug-related adverse reactions. The most commonly seen adverse reactions in U.S. trials of the tablet formulation were gastrointestinal events, which were reported in 30% of adult patients on either the BID or the QD regimen. Clinically mild gastrointestinal side effects occurred in 20% of all patients, moderate events occurred in 9% of all patients and severe adverse reactions occurred in 2% of all patients. Individual event rates included diarrhea 16%, loose or frequent stools 6%, abdominal pain 3%, nausea 7%, dyspepsia 3%, and flatulence 4%. The incidence of gastrointestinal adverse reactions, including diarrhea and loose stools, in pediatric patients receiving the suspension was comparable to the incidence seen in adult patients receiving tablets.
These symptoms usually responded to symptomatic therapy or ceased when cefixime was discontinued.
Several patients developed severe diarrhea and/or documented pseudomembranous colitis, and a few required hospitalization.
The following adverse reactions have been reported following the use of cefixime. Incidence rates were less than 1 in 50 (less than 2%), except as noted above for gastrointestinal events.

Gastrointestinal (see above): Diarrhea, loose stools, abdominal pain, dyspepsia, nausea, and vomiting. Several cases of documented pseudomembranous colitis were identified during the studies. The onset of pseudomembranous colitis symptoms may occur during or after therapy.

Hypersensitivity Reactions: Anaphylactic/anaphylactoid reactions (including shock and fatalities), skin rashes, urticaria, drug fever, pruritus, angioedema, and facial edema. Erythema multiforme, Stevens-Johnson syndrome, and serum sickness-like reactions have been reported.

Hepatic: Transient elevations in SGPT, SGOT, alkaline phosphatase, hepatitis, jaundice.

Renal: Transient elevations in BUN or creatinine, acute renal failure.

Central Nervous System: Headaches, dizziness, seizures.

Hemic and Lymphatic Systems: Transient thrombocytopenia, leukopenia, neutropenia, and eosinophilia. Prolongation in prothrombin time was seen rarely.

Abnormal Laboratory Tests: Hyperbilirubinemia.

Other: Genital pruritus, vaginitis, candidiasis, toxic epidermal necrolysis.

In addition to the adverse reactions listed above which have been observed in patients treated with cefixime, the following adverse reactions and altered laboratory tests have been reported for cephalosporin-class antibiotics:
Adverse reactions: Allergic reactions, superinfection, renal dysfunction, toxic nephropathy, hepatic dysfunction including cholestasis, aplastic anemia, hemolytic anemia, hemorrhage, and colitis.

Several cephalosporins have been implicated in triggering seizures, particularly in patients with renal impairment when the dosage was not reduced. (See **DOSAGE AND ADMINISTRATION and OVERDOSAGE**.) If seizures associated with drug therapy occur, the drug should be discontinued. Anticonvulsant therapy can be given if clinically indicated.

Abnormal Laboratory Tests: Positive direct Coombs test, elevated LDH, pancytopenia, agranulocytosis.

OVERDOSAGE
Gastric lavage may be indicated; otherwise, no specific antidote exists. Cefixime is not removed in significant quantities from the circulation by hemodialysis or peritoneal dialysis. Adverse reactions in small numbers of healthy adult volunteers receiving single doses up to 2 g of cefixime did not differ from the profile seen in patients treated at the recommended doses.

DOSAGE AND ADMINISTRATION

ALL RECOMMENDED DOSAGE FOR CEFIXIME SUSPENSION ARE INCLUDED IN THIS SECTION FOR INFORMATIONAL PURPOSE ONLY. CEFIXIME CHEWABLE TABLETS 100 MG ARE APPROPRIATE FOR A 100 MG DOSE, CEFIXIME CHEWABLE TABLETS 150 MG ARE APPROPRIATE FOR A 150 MG DOSE AND CEFIXIME CHEWABLE TABLETS 200 MG ARE APPROPRIATE FOR A 200 MG DOSE.

CEFIXIME CHEWABLE TABLETS SHOULD BE CHEWED BEFORE SWALLOWING.

Adults: The recommended dose is 400 mg daily. For the treatment of uncomplicated cervical/urethral gonococcal infections, a single oral dose of 400 mg is recommended.

Children: The recommended dose is 8 mg/kg/day of the cefixime. This may be administered as a single daily dose or may be given in two divided doses, as 4 mg/kg every 12 hours.

PEDIATRIC DOSAGE CHART			
Patient Weight (kg)	Dose/Day mg	Dose/Day mL = tsp of suspension	Cefixime Chewable Tablet Dose
6.25	50	2.5 mL = ½ tsp	---
12.5	100	5 mL =1 tsp	1 tablet of 100 mg
18.75	150	7.5 mL = 1 ½ tsp	1 tablet of 150 mg
25	200	10 mL = 2 tsp	1 tablet of 200 mg
31.25	250	12.5 mL = 2 ½ tsp	---
37.5	300	15 mL = 3 tsp	---

Children weighing more than 50 kg or older than 12 years should be treated with the recommended adult dose.

Otitis media should be treated with the cefixime chewable tablets or suspension. Clinical studies of otitis media were conducted with the cefixime chewable tablets or suspension, and the cefixime chewable tablets or suspension results in higher peak blood levels than the tablet when administered at the same dose. Therefore, the tablet should not be substituted for the cefixime chewable tablets or suspension in the treatment of otitis media. (See **CLINICAL PHARMACOLOGY**.)

Efficacy and safety in infants aged less than six months have not been established.

In the treatment of infections due to *S. pyogenes*, a therapeutic dosage of cefixime chewable tablets should be administered for at least 10 days.

Renal Impairment
Cefixime chewable tablets may be administered in the presence of impaired renal function. Normal dose and schedule may be employed in patients with creatinine clearances of 60 mL/min or greater. Patients whose clearance is between 21 and 60 mL/min or patients who are on renal hemodialysis may be given 75% of the standard dosage at the standard dosing interval (i.e., 300 mg daily). Patients whose clearance is < 20 mL/min, or patients who are on continuous ambulatory peritoneal dialysis may be given half the standard dosage at the standard dosing interval (i.e., 200 mg daily). Neither hemodialysis nor peritoneal dialysis remove significant amounts of drug from the body.

HOW SUPPLIED

Cefixime chewable tablets 100 mg, 150 mg and 200 mg.

Package sizes to be determined.

Storage: Store at 20 - 25°C (68 - 77°F) [See USP Controlled Room Temperature].

REFERENCES

1. Bauer AW, Kirby WMM, Sherris JC, et al.: Antibiotic susceptibility testing by a standard single disk method. *Am J Clin Pathol* 1966; 45:493.
2. National Committee for Clinical Laboratory Standards, Approved Standard: Performance Standards for Antimicrobial Disk Susceptibility Tests (M2-A3), December 1984.
3. Standardized disk susceptibility test. Federal Register 1974; 39 (May 30): 19182-19184.

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(Date: June 2004)

ENCLOSURE 2

Labeling of the Reference Listed Drug Product –
Cefixime for Oral Suspension USP, 100 mg/5 mL
[ANDA #65-129, Holder - Lupin Limited]

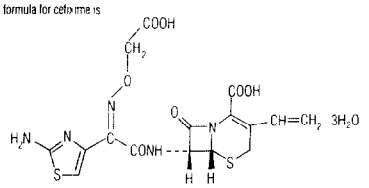
SUPRAX®
CEFIXIME FOR ORAL SUSPENSION, USP 100 mg/5 mL
Rx only

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Suprax (cefixime) for Oral Suspension and other antibacterial drugs, Suprax should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

DESCRIPTION

Suprax (cefixime) for Oral Suspension is a semisynthetic cephalosporin antibiotic for oral administration. Chemically it is (6*R*,7*R*)-7-[2-(2-Amino-4-thiazolyl)glyoxylamido]-8-oxo-3-vinyl-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 7²-(*Z*)-[*O*-(carboxymethyl) oxime] trihydrate.
Molecular weight = 507.50 as the trihydrate

The structural formula for cefixime is



After reconstitution each teaspoonful (5 mL) of suspension contains 100 mg of cefixime as the trihydrate. In addition, the suspension contains the following inactive ingredients: strawberry flavor, sodium benzoate, sucrose, colloidal silicon dioxide and xanthan gum.

CLINICAL PHARMACOLOGY

Suprax given orally is about 40%-50% absorbed whether administered with or without food; however, time to maximal absorption is increased approximately 0.8 hours when administered with food. The oral suspension produces average peak concentrations approximately 25%-50% higher than the tablets when tested in normal *adult* volunteers. Two hundred and 400 mg doses of oral suspension produce average peak concentrations of 3 mcg/mL (range 1 to 4.5 mcg/mL) and 4.6 mcg/mL (range 1.9 to 7.7 mcg/mL), respectively when tested in normal *adult* volunteers. The area under the time versus concentration curve is greater by approximately 10%-25% with the oral suspension than with the tablet after doses of 100 to 400 mg, when tested in normal *adult* volunteers. This increased absorption should be taken into consideration if the oral suspension is to be substituted for the tablet. Because of the lack of bioequivalence, tablets should not be substituted for oral suspension in the treatment of otitis media. (See **DOSAGE AND ADMINISTRATION**)
Cross-over studies of tablet versus suspension have not been performed in children.
Peak serum concentrations occur between 2 and 6 hours following oral administration of 400 mg of Cefixime suspension.
Peak serum concentrations occur between 2 and 5 hours following a single administration of 200 mg of suspension.

TABLE

Serum Levels of Cefixime after Administration of Tablets (mcg/mL)

DOSE	1h	2h	4h	6h	8h	12h	24h
100 mg	0.3	0.8	1	0.7	0.4	0.2	0.02
200 mg	0.7	1.4	2	1.5	1	0.4	0.03
400 mg	1.4	2.5	3.5	2.7	1.7	0.6	0.04

Serum Levels of Cefixime after Administration of Oral Suspension (mcg/mL)

DOSE	1h	2h	4h	6h	8h	12h	24h
100 mg	0.7	1.1	1.3	0.9	0.6	0.2	0.02
200 mg	1.2	2.1	2.8	2	1.3	0.5	0.07
400 mg	1.8	3.3	4.4	3.3	2.2	0.8	0.07

Approximately 50% of the absorbed dose is excreted unchanged in the urine in 24 hours. In animal studies, it was noted that cefixime is also excreted in the bile in excess of 10% of the administered dose. Serum protein binding is concentration independent with a bound fraction of approximately 65%. In a multiple dose study conducted with a research formulation which is less bioavailable than the tablet or suspension, there was little accumulation of drug in serum or urine after dosing for 14 days. The serum half-life of cefixime in healthy subjects is independent of dosage form and averages 3-4 hours but may range up to 9 hours in some normal volunteers. Average AUCs at steady state in elderly patients are approximately 40% higher than average AUCs in other healthy adults.

In subjects with moderate impairment of renal function (20 to 40 mL/min creatinine clearance), the average serum half-life of cefixime is prolonged to 6.4 hours. In severe renal impairment (5 to 20 mL/min creatinine clearance), the half-life increased to an average of 11.5 hours. The drug is not cleared significantly from the blood by hemodialysis or peritoneal dialysis. However, a study indicated that with doses of 400 mg, patients undergoing hemodialysis have similar blood profiles as subjects with creatinine clearances of 21-60 mL/min. There is no evidence of metabolism of cefixime *in vivo*.

Adequate data on CSF levels of cefixime are not available.

Microbiology

As with other cephalosporins, bactericidal action of cefixime results from inhibition of cell-wall synthesis. Cefixime is highly stable in the presence of beta-lactamase enzymes. As a result, many organisms resistant to penicillins and some cephalosporins due to the presence of beta-lactamases may be susceptible to cefixime. Cefixime has been shown to be active against most strains of the following organisms both *in vitro* and in clinical infections (see **INDICATIONS AND USAGE**):

Gram-positive Organisms
Streptococcus pneumoniae
Streptococcus pyogenes
Gram-negative Organisms
Haemophilus influenzae
(beta-lactamase positive and negative strains)
Moraxella (Branhamella) catarrhalis
(most of which are beta-lactamase positive),
Escherichia coli
Proteus mirabilis
Neisseria gonorrhoeae
(including penicillinase- and non-penicillinase producing strains)

Cefixime has been shown to be active *in vitro* against most strains of the following organisms; however, clinical efficacy has not been established.

Gram-positive Organisms
Streptococcus agalactiae
Gram-negative Organisms
Haemophilus parainfluenzae
(beta-lactamase positive and negative strains)
Proteus vulgaris
Klebsiella pneumoniae
Klebsiella oxytoca
Pasteurella multocida
Providencia species
Salmonella species
Shigella species
Citrobacter amalonaticus
Citrobacter diversus
Serratia marcescens

Note: *Pseudomonas* species, strains of group D streptococci (including enterococci), *Listeria monocytogenes*, most strains of staphylococci (including methicillin-resistant strains) and most strains of *Enterobacter* are resistant to cefixime. In addition, most strains of *Bacteroides fragilis* and *Clostridia* are resistant to cefixime.

Susceptibility Testing
Susceptibility Tests
Diffusion Techniques

Quantitative methods that require measurement of zone diameters give an estimate of antibiotic susceptibility. One such procedure[1,3] has been recommended for use with disks to test susceptibility to cefixime. Interpretation involves correlation of the diameters obtained in the disk test with the minimum inhibitory concentration (MIC) for cefixime.

Reports from the laboratory giving results of the standard single-disk susceptibility test with a 5-mcg cefixime disk should be interpreted according to the following criteria:

Recommended Susceptibility Ranges, Agar Disk Diffusion

Organisms	Resistant	Moderately Susceptible	Susceptible
Neisseria gonorrhoeae[a]	--	--	≥ 31 mm
All other organisms	≤ 15 mm	16 - 18 mm	≥ 19 mm

[a] Using GC Agar Base with a defined 1% supplement without cysteine

A report of "Susceptible" indicates that the pathogen is likely to be inhibited by generally achievable blood levels. A report of "Moderately Susceptible" indicates that inhibitory concentrations of the antibiotic may well be achieved if high dosage is used or if the infection is confined to tissues and fluids (e.g. urine) in which high antibiotic levels are attained. A report of "Resistant" indicates that achievable concentrations of the antibiotic are unlikely to be inhibitory and other therapy should be selected.

Standardized procedures require the use of laboratory control organisms. The 5 mcg disk should give the following zone diameter:

Organism	Zone diameter (mm)
E. coli ATCC 25922	23-27
N. gonorrhoeae ATCC 49226[a]	37-45

[a] Using GC Agar Base with a defined 1% supplement without cysteine

The class disk for cephalosporin susceptibility testing (the cephalothin disk) is not appropriate because of spectrum differences with cefixime. The 5-mcg cefixime disk should be used for all *in vitro* testing of isolates.

Dilution Techniques

Broth or agar dilution methods can be used to determine the minimum inhibitory concentration (MIC) value for susceptibility of bacterial isolates to cefixime. The recommended susceptibility breakpoints are as follows:

MIC Interpretive Standards (mcg/mL)

Organisms	Resistant	Moderately Susceptible	Susceptible
Neisseria gonorrhoeae[a]	--	--	≤ 0.25
All other organisms	≥ 4	2	≤ 1

As with standard diffusion methods, dilution procedures require the use of laboratory control organisms. Standard cefixime powder should give the following MIC ranges in daily testing of quality control organisms:

Organism	MIC range (mcg/mL)
E. coli ATCC 25922	0.25-1
S. aureus ATCC 29213	8-32
N. gonorrhoeae ATCC 49226[a]	0.008-0.03

[a] Using GC Agar Base with a defined 1% supplement without cysteine

INDICATIONS AND USAGE

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Suprax (cefixime) for Oral Suspension and other antibacterial drugs, Suprax should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antimicrobial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

Suprax is indicated in the treatment of the following infections when caused by susceptible strains of the designated microorganisms:

Uncomplicated Urinary Tract Infections caused by *Escherichia coli* and *Proteus mirabilis*.

Otitis Media caused by *Haemophilus influenzae* (beta-lactamase positive and negative strains), *Moraxella (Branhamella) catarrhalis* (most of which are beta-lactamase positive) and *S. pyogenes*.*
Note: For information on *otitis media* caused by *Streptococcus pneumoniae*, see **CLINICAL STUDIES** section.

Pharyngitis and Tonsillitis caused by *S. pyogenes*.
Note: Penicillin is the usual drug of choice in the treatment of *S. pyogenes* infections, including the prophylaxis of rheumatic fever. Suprax is generally effective in the eradication of *S. pyogenes* from the nasopharynx; however, data establishing the efficacy of Suprax in the subsequent prevention of rheumatic fever are not available.

Acute Bronchitis and Acute Exacerbations of Chronic Bronchitis caused by *Streptococcus pneumoniae* and *Haemophilus influenzae* (beta-lactamase positive and negative strains).

Uncomplicated gonorrhea (cervical/urethral), caused by *Neisseria gonorrhoeae* (penicillinase-and non-penicillinase producing strains).

Appropriate cultures and susceptibility studies should be performed to determine the causative organism and its susceptibility to cefixime; however, therapy may be started while awaiting the results of these studies. Therapy should be adjusted, if necessary, once these results are known.

* Efficacy for this organism in this organ system was studied in fewer than 10 infections.

CLINICAL STUDIES

In clinical trials of otitis media in nearly 400 children between the ages of 6 months to 10 years, *Streptococcus pneumoniae* was isolated from 47% of the patients, *Haemophilus influenzae* from 34%, *Moraxella (Branhamella) catarrhalis* from 15% and *S. pyogenes* from 4%.

The overall response rate of *Streptococcus pneumoniae* to cefixime was approximately 10% lower and that of *Haemophilus influenzae* or *Moraxella (Branhamella) catarrhalis* approximately 7% higher (12% when beta-lactamase positive strains of *H. influenzae* are included) than the response rates of these organisms to the active control drugs.

In these studies, patients were randomized and treated with either cefixime at dose regimens of 4 mg/kg BID or 8 mg/kg QD or with a standard antibiotic regimen. Sixty-nine to 70% of the patients in each group had resolution of signs and symptoms of otitis media when evaluated 2 to 4 weeks post-treatment, but persistent effusion was found in 15% of the patients. When evaluated at the completion of therapy, 17% of patients receiving cefixime and 14% of patients receiving effective comparative drugs (18% including those patients who had *Haemophilus influenzae* resistant to the control drug and who received the control antibiotic) were considered to be treatment failures. By the 2 to 4 week follow up, a total of 30%-31% of patients had evidence of either treatment failure or recurrent disease.

Bacteriological Outcome of Otitis Media at Two to Four Weeks Post-Therapy Based on Repeat Middle Ear Fluid Culture or Extrapolation from Clinical Outcome

Organism	Cefixime(a) 4 mg/kg BID	Cefixime(a) 8 mg/kg QD	Control(a) drugs
Streptococcus pneumoniae	48/70 (69%)	18/22 (82%)	82/100 (82%)
Haemophilus influenzae beta-lactamase negative	24/34 (71%)	13/17 (76%)	23/34 (68%)
Haemophilus influenzae beta-lactamase positive	17/22 (77%)	9/12 (75%)	1/1 (b)
Moraxella (Branhamella) catarrhalis	26/31 (84%)	5/5	18/24 (75%)
S. pyogenes	5/5	3/3	6/7
All Isolates	120/162 (74%)	48/59 (81%)	130/166 (78%)

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a) Number eradicated/number isolated

b) An additional 20 beta-lactamase positive strains of *Haemophilus influenzae* were originally isolated but were excluded from this analysis because they were resistant to the control antibiotic. In nineteen of these, the clinical course could be assessed and a favorable outcome occurred in 10. When these cases are included in the overall bacteriological evaluation of therapy with the control drugs, 140/185 (76%) of pathogens were considered to be eradicated.

CONTRAINDICATIONS

Suprax is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

WARNINGS

BEFORE THERAPY WITH SUPRAX IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE TO DETERMINE WHETHER THE PATIENT HAS HAD PREVIOUS HYPERSENSITIVITY REACTIONS TO CEPHALOSPORINS, PENICILLINS, OR OTHER DRUGS. IF THIS PRODUCT IS TO BE GIVEN TO PENICILLIN-SENSITIVE PATIENTS, CAUTION SHOULD BE EXERCISED BECAUSE CROSS HYPERSENSITIVITY AMONG BETA-LACTAM ANTIBIOTICS HAS BEEN CLEARLY DOCUMENTED AND MAY OCCUR IN UP TO 10% OF PATIENTS WITH A HISTORY OF PENICILLIN ALLERGY. IF AN ALLERGIC REACTION TO SUPRAX OCCURS, DISCONTINUE THE DRUG. SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE TREATMENT WITH EPINEPHRINE AND OTHER EMERGENCY MEASURES, INCLUDING OXYGEN, INTRAVENOUS FLUIDS, INTRAVENOUS ANTIHISTAMINES, CORTICOSTEROIDS, PRESSOR AMINES AND AIRWAY MANAGEMENT, AS CLINICALLY INDICATED.

Anaphylactic/anaphylactoid reactions (including shock and fatalities) have been reported with the use of cefixime.

Antibiotics, including Suprax, should be administered cautiously to any patient who has demonstrated some form of allergy, particularly to drugs.

Treatment with broad spectrum antibiotics, including Suprax, alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is a primary cause of severe antibiotic-associated diarrhea including pseudomembranous colitis.

Pseudomembranous colitis has been reported with the use of Suprax and other broad spectrum antibiotics (including macrolides, semisynthetic penicillins, and cephalosporins); therefore, it is important to consider this diagnosis in patients who develop diarrhea in association with the use of antibiotics. Symptoms of pseudomembranous colitis may occur during or after antibiotic treatment and may range in severity from mild to life-threatening. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, management should include fluids, electrolytes, and protein supplementation. If the colitis does not improve after the drug has been discontinued, or if the symptoms are severe, oral vancomycin is the drug of choice for antibiotic-associated pseudomembranous colitis produced by *C. difficile*. Other causes of colitis should be excluded.

PRECAUTIONS

General

Prescribing Suprax (cefixime for Oral Suspension) in the absence of a proven or strongly suspected bacterial infection of a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

The possibility of the emergence of resistant organisms which might result in overgrowth should be kept in mind, particularly during prolonged treatment. In such use, careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.

The dose of Suprax should be adjusted in patients with renal impairment as well as those undergoing continuous ambulatory peritoneal dialysis (CAPD) and hemodialysis (HD). Patients on dialysis should be monitored carefully. (See **DOSAGE AND ADMINISTRATION**.)

Suprax should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis.

Drug Interactions

Carbamazepine: Elevated carbamazepine levels have been reported in postmarketing experience when cefixime is administered concomitantly. Drug monitoring may be of assistance in detecting alterations in carbamazepine plasma concentrations.

Warfarin and Anticoagulants: Increased prothrombin time, with or without clinical bleeding, has been reported when cefixime is administered concomitantly.

Drug/Laboratory Test Interactions

A false-positive reaction for ketones in the urine may occur with tests using nitroprusside but not with those using nitroferricyanide.

The administration of cefixime may result in a false-positive reaction for glucose in the urine using Clinitest®**, Benedict's solution, or Fehling's solution. It is recommended that glucose tests based on enzymatic glucose oxidase reactions (such as Clinistix®** or TesTape®**) be used.

A false positive direct Coombs test has been reported during treatment with other cephalosporin antibiotics; therefore, it should be recognized that a positive Coombs test may be due to the drug.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Lifetime studies in animals to evaluate carcinogenic potential have not been conducted. Cefixime did not cause point mutations in bacteria or mammalian cells. DNA damage, or chromosome damage *in vitro* and did not exhibit clastogenic potential, *in vivo* in the mouse micronucleus test. In rats, fertility and reproductive performance were not affected by cefixime at doses up to 125 times the adult therapeutic dose.

Usage in Pregnancy

Pregnancy Category B. Reproduction studies have been performed in mice and rats at doses up to 400 times the human dose and have revealed no evidence of harm to the fetus due to cefixime. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery

Cefixime has not been studied for use during labor and delivery. Treatment should only be given if clearly needed.

Nursing Mothers

It is not known whether cefixime is excreted in human milk. Consideration should be given to discontinuing nursing temporarily during treatment with this drug.

Pediatric Use

Safety and effectiveness of cefixime in children aged less than six months old have not been established.

The incidence of gastrointestinal adverse reactions, including diarrhea and loose stools, in the pediatric patients receiving the suspension was comparable to the incidence seen in adult patients receiving tablets.

Information for Patients

Patients should be counseled that antibacterial drugs, including Suprax, should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When Suprax is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by Suprax or other antibacterial drugs in the future.

ADVERSE REACTIONS

Most of adverse reactions observed in clinical trials were of a mild and transient nature. Five percent (5%) of patients in the U.S. trials discontinued therapy because of drug-related adverse reactions. The most commonly seen adverse reactions in U.S. trials of the tablet formulation were gastrointestinal events, which were reported in 30% of adult patients on either the BID or the QD regimen. Clinically mild gastrointestinal side effects occurred in 20% of all patients; moderate events occurred in 9% of all patients and severe adverse reactions occurred in 2% of all patients. Individual event rates included diarrhea 16%, loose or frequent stools 6%, abdominal pain 3%, nausea 7%, dyspepsia 3%, and flatulence 4%.

The incidence of gastrointestinal adverse reactions, including diarrhea and loose stools, in pediatric patients receiving the suspension was comparable to the incidence seen in adult patients receiving tablets.

These symptoms usually responded to symptomatic therapy or ceased when cefixime was discontinued.

Several patients developed severe diarrhea and/or documented pseudomembranous colitis, and a few required hospitalization.

The following adverse reactions have been reported following the use of cefixime; incidence rates were less than 1 in 50 (less than 2%), except as noted above for gastrointestinal events.

Gastrointestinal (see above): Diarrhea, loose stools, abdominal pain, dyspepsia, nausea, and vomiting. Several cases of documented pseudomembranous colitis were identified during the studies. The onset of pseudomembranous colitis symptoms may occur during or after therapy.

Hypersensitivity Reactions: Anaphylactic/anaphylactoid reactions (including shock and fatalities), skin rashes, urticaria, drug fever, pruritus, angioedema, and facial edema. Erythema multiforme, Stevens-Johnson syndrome, and serum sickness-like reactions have been reported.

Hepatic: Transient elevations in SGPT, SGOT, alkaline phosphatase, hepatitis, jaundice.

Renal: Transient elevations in BUN or creatinine, acute renal failure.

Central Nervous System: Headaches, dizziness, seizures.

Hemic and Lymphatic Systems: Transient thrombocytopenia, leukopenia, neutropenia, and eosinophilia. Prolongation of prothrombin time was seen rarely.

Abnormal Laboratory Tests: Hyperbilirubinemia.

Other: Genital pruritus, vaginitis, candidiasis, toxic epidermal necrolysis.

In addition to the adverse reactions listed above which have been observed in patients treated with cefixime, the following adverse reactions and altered laboratory tests have been reported for cephalosporin-class antibiotics:

Adverse reactions: Allergic reactions, superinfection, renal dysfunction, toxic nephropathy, hepatic dysfunction including cholestasis, aplastic anemia, hemolytic anemia, hemorrhage, and colitis.

Several cephalosporins have been implicated in triggering seizures, particularly in patients with renal impairment when the dosage was not reduced. (See **DOSAGE AND ADMINISTRATION** and **OVERDOSAGE**.) If seizures associated with drug therapy occur, the drug should be discontinued. Anticonvulsant therapy can be given if clinically indicated.

Abnormal Laboratory Tests: Positive direct Coombs test, elevated LDH, pancytopenia, agranulocytosis.

OVERDOSAGE

Gastric lavage may be indicated, otherwise, no specific antidote exists. Cefixime is not removed in significant quantities from the circulation by hemodialysis or peritoneal dialysis. Adverse reactions in small numbers of healthy adult volunteers receiving single doses up to 2 g of cefixime did not differ from the profile seen in patients treated at the recommended doses.

DOSAGE AND ADMINISTRATION

Adults: Once Suprax is reconstituted, the recommended dose of the suspension is 400 mg daily. For the treatment of uncomplicated cervical/urethral gonococcal infections, a single oral dose of 400 mg is recommended.

Children: The recommended dose is 8 mg/kg/day of the suspension. This may be administered as a single daily dose or may be given in two divided doses, as 4 mg/kg every 12 hours.

PEDIATRIC DOSAGE CHART

Patient Weight (kg)	Dose/Day mg	Dose/Day mL	Dose/Day tsp of suspension
6.25	50	2.5	½
12.5	100	5	1
18.75	150	7.5	1½
25	200	10	2
31.25	250	12.5	2½
37.5	300	15	3

Children weighing more than 50 kg or older than 12 years should be treated with the recommended adult dose.

Otitis media should be treated with the suspension. Clinical studies of otitis media were conducted with the suspension and the suspension results in higher peak blood levels than the tablet when administered at the same dose. Therefore, the tablet should not be substituted for the suspension in the treatment of otitis media. (See **CLINICAL PHARMACOLOGY**.)

Efficacy and safety in infants aged less than six months have not been established.

In the treatment of infections due to *S. pyogenes*, a therapeutic dosage of Suprax should be administered for at least 10 days.

Renal Impairment

Suprax may be administered in the presence of impaired renal function. Normal dose and schedule may be employed in patients with creatinine clearances of 60 mL/min or greater. Patients whose clearance is between 21 and 60 mL/min or patients who are on renal hemodialysis may be given **75%** of the standard dosage at the standard dosing interval (i.e., 300 mg daily). Patients whose clearance is < 20 mL/min, or patients who are on continuous ambulatory peritoneal dialysis may be given half the standard dosage at the standard dosing interval (i.e., 200 mg once daily). Neither hemodialysis nor peritoneal dialysis remove significant amounts of drug from the body.

Reconstitution Directions For Oral Suspension

Bottle Size	Reconstitution Directions
100 mL 100 mg/5 mL	To reconstitute, suspend with **68 mL water**. Method: Tap the bottle several times to loosen powder contents prior to reconstitution. Add approximately half the total amount of water for reconstitution and shake well. Add the remainder of water and shake well.
75 mL 100 mg/5 mL	To reconstitute, suspend with **51 mL water**. Method: Tap the bottle several times to loosen powder contents prior to reconstitution. Add approximately half the total amount of water for reconstitution and shake well. Add the remainder of water and shake well.
50 mL 100 mg/5 mL	To reconstitute, suspend with **34 mL water**. Method: Tap the bottle several times to loosen powder contents prior to reconstitution. Add approximately half the total amount of water for reconstitution and shake well. Add the remainder of water and shake well.

After reconstitution the suspension may be kept for 14 days either at room temperature or under refrigeration without significant loss of potency. Keep tightly closed. Shake well before using. Discard unused portion after 14 days.

HOW SUPPLIED

Suprax® (cefixime) for Oral Suspension is an off-white to pale yellow colored powder. After reconstituted as directed, each 5 mL of reconstituted suspension contains 100 mg of cefixime as the trihydrate. Suprax is supplied as follows:

NDC 68180-202-03 - 50 mL Bottle
NDC 68180-202-02 - 75 mL Bottle
NDC 68180-202-01 - 100 mL Bottle

Prior to reconstitution: Store drug powder at 20 – 25°C (68 – 77°F) [See USP Controlled Room Temperature]
After reconstitution, Store at room temperature or under refrigeration
Keep tightly closed

REFERENCES

1. Bauer AW, Kirby WMM, Sherris JC, et al: Antibiotic susceptibility testing by a standard single disk method. *Am J Clin Pathol* 1966; 45: 493.
2. National Committee for Clinical Laboratory Standards: Approved Standard: Performance Standards for Antimicrobial Disk Susceptibility Tests (M2-A3), December 1984.
3. Standardized disk susceptibility test/ *Federal Register* 1974; 39 (May 30): 19182-19184.

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